Remarks

The February 26, 2008, Official Action and the references cited therein have been carefully reviewed. In view of the amendments presented herewith and the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset, it is noted that a shortened statutory response period of three (3) months was set forth in the February 26, 2008, Official Action. Therefore, the initial due date for response was May 26, 2008. A petition for three (3) months extension of time is presented with this response, which is being filed within the three month extension period.

As a preliminary matter, Applicants note that the Examiner prosecuting this application has been changed, and that the rejection set forth in the February 26, 2008, Official Action is the only rejection pending in the instant application. Accordingly, claims 1-2, 24, 28 and 43 are pending and have been examined on the merits.

Turning to the substantive aspects of the February 26, 2008, Official Action, at page 3, the Examiner has rejected claims 1, 2, 24, 28 and 43 under 35 U.S.C. §112, first paragraph, for alleged failing to comply with the enablement requirement.

In accordance with the instant amendment, claim 44 has been added. Support for new claim 44 can be found throughout the specification including, for example, original claim 12. No new matter has been introduced into this application by reason of any of the amendments presented herewith.

In view of the present amendment and the reasons set forth in this response, Applicants respectfully submit that the 35 U.S.C. §112, first paragraph rejection of claims 1, 2, 24, 28 and 43, as set forth in the February 26, 2008 Official Action, cannot be maintained. This ground of rejection is, therefore, respectfully traversed.

CLAIMS 1, 2, 24, 28 AND 43 SATISFIY THE ENABLEMENMT REQUIREMENT OF 35 U.S.C. §112, FIRST PARAGRAPH

The Examiner has rejected claims 1, 2, 24, 28 and 43 under 35 U.S.C. §112, first paragraph. Specifically, the Examiner asserts that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The Examiner has applied the enablement factors provided at §2164.01(a) of the MPEP and In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988), and concluded that a skilled artisan would have to perform undue experimentation to practice the full scope of the claimed invention.

Applicants strenuously disagree with the Examiner's position for the reasons set forth below. First, in In re Wands, the Federal Circuit held that engaging in experimentation to practice a claimed invention does not render the disclosure non-enabling as long as the experimentation required is not "undue." The Court stated that: "The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness . . . The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 8 USPQ2d at 1404. Indeed, "the mere fact that experimentation may have been difficult and time consuming does not mandate a conclusion that such experimentation would have been considered 'undue'." Falkner v. Inglis, 448 F.3d 1357, 1365 (Fed. Cir. 2006).

Applicants also refer the Examiner to MPEP §2164.05(a) which states:

> In general, the examiner should not use post-filing date references to demonstrate that the patent is non-enabling. Exceptions to this rule could occur if a

> later-dated reference provides evidence of what one skilled in the art would have known on or before the effective filing date of the patent application. In re Hogan, 559 F.2d 595, 605, 194 USPQ 527, 537 (CCPA 1977).

Indeed, the court in In re Hogan further stated that they "approved use of later publications as evidence of the state of art existing on the filing date of an application. That approval does not extend, however, to the use of a later ... publication disclosing a later existing state of the art in testing an earlier application for compliance with §112, first paragraph." The court concluded that it was impermissible to apply "later knowledge about later art-related facts." Notably, the Examiner has relied almost exclusively on post-filing references which disclose a later existing state of the art in order to arrive at the instant enablement rejection.

The instant claims are drawn to methods of "preventing the formation of inhibitory antibodies to Factor IX delivered to a mammal by way of an adeno-associated viral vector, wherein said mammal has a genetic defect which can result in generation of inhibitory antibodies to Factor IX, said method comprising intravenously or intraperitoneally administering to said mammal cyclophosphamide prior to or simultaneously with said adeno-associated viral vector delivery before formation of said inhibitory antibodies, the delivered Factor IX being from the same species as said mammal." Further, the instant specification incorporates by reference numerous publications which describe gene therapy with adeno-associated viral vectors encoding Factor IX (see, e.g., page 6, lines 4-15). As such, the instant application clearly provides the skilled artisan with guidance as to how to make and use the instant invention.

At the outset, the Examiner is respectfully reminded that the Applicants have previously submitted data which clearly demonstrates that, in a canine model, the administration of cyclophosphamide with Factor IX gene therapy was effective at

"preventing the formation of inhibitory antibodies to Factor IX", as instantly claimed (see October 23, 2006 Official Action response and Exhibit A provided therewith). Indeed, no inhibitory antibodies against FIX were detected in all ten dogs which received cyclophosphamide with FIX gene therapy. In contrast, when cyclophosphamide was not administered, inhibitory antibodies to FIX were detected in two of the three dogs. It is also noteworthy that the lack of inhibitory antibodies was long-term as inhibitory antibodies were not detected several years after the initial administration. It is also significant that these animals are still expressing FIX years after AAV administration and have had their hemophilic bleeding disorder at least partially corrected (see, e.g., Arruda et al. (Blood (2005) 105:3458-3464). In view of the foregoing, it is evident that the instantly claimed methods have been fully demonstrated in both a small scale mammal model (mice, see instant application) and a large scale mammal model (canine). The effectiveness of the instantly claimed methods on such diverse members of the mammalian class of animals clearly indicates that the instant claims are fully enabled for all mammals.

Applicants also submit herewith Jiang et al. (Molecular Therapy (2006) 14:452-455) which discloses the results from a phase I clinical trial of FIX gene therapy on humans. Briefly, eight human hemophilia patients were administered an adeno-associated viral vector encoding FIX (see, e.g., page 452). Jiang et al. teach that FIX expression continued for at least 10 months and that the FIX transgene was still present 3.7 years following AAV treatment (see, e.g., Abstract). Thus, Jiang et al. present data substantiating Applicants teaching that Factor IX can be delivered to human patients with the expression of the transgene sustained well beyond the time of delivery. This finding fundamentally disproves the basis on which the Office is relying in making the instant rejection. It is also noteworthy that the human patient that

was followed up with (Subject H) reported a decrease in bleeding episodes, thereby indicating that the administration of FIX via an AAV vector (gene therapy) resulted in a correction/amelioration of the hemophilic bleeding condition (see page 453).

Jiang et al. also conclude by stating that the study has demonstrated "multiyear AAV-2 mediated FIX gene transfer and expression in a human subject, similar to findings in dogs that maintained FIX expression >4 years after AAV2 vector delivery" (see page 455, left column, second full paragraph). Notably, the canine work alluded to in this conclusion is the work described in Arruda et al., discussed herein. Thus, the connection between the canine hemophilia model and humans is readily apparent and it shows that gene therapy with Factor IX is not unpredictable.

In view of the foregoing, it is without question that the instantly claimed methods are fully enabled. Indeed, Applicants have demonstrated the instant methods in both a canine and a mouse model of hemophilia and have demonstrated that the use of AAV vectors encoding FIX (even without an immunosuppressant such as cyclophosphamide) can yield long-term expression of FIX. Furthermore, although not expressly required by the instant claims, the administration of an AAV vector encoding FIX to a human can at least partially correct hemophilia B in a human patient. It is without question a skilled artisan, apprised of the instant application, would expect the co-administration of the immunosuppressant cyclophosphamide would result in even greater benefits for humans administered AAV vectors encoding FIX. Indeed, as of the effective filing date of the instant application, a reasonable correlation existed between the in vivo mouse model of hemophilia described in the instant application and other mammals such as humans. This is supported by the success of the instantly claimed methods in both dogs and humans.

At pages 4-13 of the instant Official Action, the

Examiner cites several references, most of which are post-filing references, and contends that gene therapy is not generally enabled. Applicants respectfully disagree for the reasons set forth below.

First, the Examiner cites Kay et al., but states that the reference does not teach the use of immunosuppressive agents for the purpose of inhibiting antibody development directed against the transgene encoding the therapeutic protein. As such, Applicants submit that this is an unrelated teaching not relevant to the instantly claimed invention.

At page 5 of the Official Action, the Examiner cites the post-filing references Kaiser (Science (2007) 317:580) and Chao et al. (Mt. Sinai J. Med. (2004) 71:305-313) for their descriptions of the progress and failures in achieving desired effects after human gene therapy. Kaiser generally speculates about what could have caused a patient's death in a gene therapy trial. Notably, the AAV vector administered encoded TNFα and Kaiser is silent with regard to FIX administration. As such, Kaiser is irrelevant to the enablement of the instantly claimed methods. Indeed, as stated hereinabove, AAV vectors encoding FIX have been safely administered to humans.

With regard to Chao et al., it is stated at page 310 that "preliminary studies demonstrate that rAAV1 vectors may bring about a dramatic increase in FIX expression after transducing skeletal muscle in large animal models, thus leading to successful gene therapy for hemophilia B" (page 310, column 2, first paragraph spanning from column 1). While the referenced studies were for the expression of FIX via an AAV vector for the treatment of hemophilia without the co-administration of an immunosuppressant such as cyclophosphamide, Chao et al. clearly points to the ability to express FIX from an AAV in a mammal.

At page 6 of the Official Action, the Examiner also cites Walsh (Gene Therapy (2003) 10:999-1003). Applicants note that the Examiner has misquoted Walsh. Indeed, the Examiner has

provided a quote at the page of 6 of the Official Action, but the quoted statement does not appear in Walsh at the indicated page and line numbers. In fact, the study referenced in the section cited by the Examiner (page 1001, column 2, second paragraph) was halted and the findings were unresolved.

The Examiner also cites Walsh as teaching that the amount of FIX expressed in mice is different than in dogs when expressed from an AAV vector. For example, the Examiner notes that "supraphysiologic levels of FIX (300% of normal)" were obtained in mice, but an equivalent dose for dogs yielded "factor IX levels around 5% of normal." At the outset, it was well within the ability of a skilled artisan as of the filing date of the instant invention to modify the dosage and or amount of AAV vector administered to a mammal in order to alter the amount of transgene expressed. Such modifications are routine and cannot reasonably be considered to require undue experimentation by the skilled artisan.

Additionally, it should be noted that, in terms of the level of Factor IX expression obtained, only very low levels need to be reached in order to demonstrate a therapeutic effect. Indeed, it was known as of the effective filing date of the instant application that the improvement of FIX levels to at least 1% of normal in humans results in the improvement of hemophilic symptoms and can prevent most spontaneous and life-threatening bleeding episodes (see Lofqvist et al. (J. Int. Med. (1997) 241:395-400; submitted herewith). Accordingly, the production of FIX levels "around 5% of normal," would be expected by a skilled artisan to be satisfactory and lead to the treatment/amelioration of hemophilic symptoms in patients.

At page 7 of the Official Action, the Examiner asserts that the "specification fails to correlate the data obtained in [sic] rodent model to any other model that could be extrapolated to the breadth of the claims." In this regard, the Examiner's attention is also respectfully drawn to In re

Strahilevitz, 212 USPQ 561 (CCPA 1982), wherein the court held that a broad immunological method claim having "nearly universal applicability" was enabled even without working examples. Cases like Strahilevitz hold that an adequate description of purely conceptual inventive work can meet the requirements of 35 U.S.C. §112 and allows inventors to file patents before obtaining working examples. The MPEP also recognizes the acceptability of prophetic examples in §608.01(p)(II) stating that "[s]imulated or predicted test results and prophetic examples (paper examples) are permitted in patent applications ... Paper examples describe the manner and process of making an embodiment of the invention which has not actually been conducted." In re Borkowski, 164 USPQ 642 (CCPA 1970), is also enlightening on this point, there the court stated "[A] specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation." The Examiner is respectfully reminded that an Applicant is entitled to claim the full scope of what was invented.

Further, the Examiner alleges at page 7 of the Official Action that the "specification fails to provide any guidance as to how the claimed method would have been practiced." The Examiner also states at page 8 of the Official Action that "the guidance provided in the specification is limited to intramuscular injection of AAVmFIX ($1x10^{11}$)." These statements by the Examiner are clearly incorrect. Indeed, at page 6, the instant application refers to numerous publications describing AAV vector mediated gene transfer of FIX. These references were also incorporated by reference (see page 16, lines 7-8). As just one example of the disclosures of these references, PCT/US98/04790 (which is cited at page 6, line 5) describes dosing amounts and routes of administration for an AAV vector encoding FIX. Accordingly, it is evident that the instant application clearly provides extensive guidance to the skilled

artisan as to how to make and use the instantly claimed invention.

Applicants note that Examiner acknowledges at pages 7-8 of the Official Action that Arruda et al. (Blood (2004) 103:85-92) show that transient immunosuppression with cyclophosphamide prevented inhibitory antibody formation in canines administered an AAV vector encoding FIX. Accordingly, the Examiner has acknowledged that the instantly claimed methods, as described in the instant application, are effective in canine.

The Examiner also cites Arruda et al. (Blood (2005) 105:3458-3464). The Examiner contends that Arruda et al. (2005) teach "that peripheral intravenous delivery of rAAV to a hemophilia B dog results in subtherapeutic FIX levels." Applicants respectfully disagree. Arruda et al. (2005) states "it seems unlikely that the procedure will be successful as a simple intravenous infusion" with the particular AAV serotype used. There is no teaching that the FIX levels are sub-therapeutic in the cited passage. Indeed, Table 1 and Figure 3B of Arruda et al. demonstrates that the dog which received the AAV vector encoding FIX intravenously accompanied by the short-term administration of cyclophosphamide had reduced clotting times compared to controls and exhibited no inhibitory antibodies to FIX. Accordingly, Arruda et al. clearly teach that the administration of an AAV vector encoding FIX to a canine intravenously with cyclophosphamide prevented the formation of inhibitory antibodies to Factor IX, as required by the claims. Furthermore, the administration resulted in a partial correction of the hemophilic symptoms of the dog. Therefore, even the Examiner's higher standards of treating hemophilia have been met.

The Examiner cites Ponder (Curr. Opin. Hematol. (2006) 13:301-307) at page 9 of the Official Action for the description that therapies effective in mice often fail in humans, and the reference mentions that there are difficulties

in scaling up to larger animals, and these difficulties may be due to the biology of animals with a longer life span. In view of all of the above, particularly the demonstration of the instantly claimed methods in canine and human subjects, it is evident the general speculations about gene therapy set forth in Ponder are irrelevant to the enablement of the instantly claimed invention. It is noteworthy, however, that Ponder state that the administration of an AAV vector encoding FIX to a human "achieved ~10% of normal activity" (see page 305). Ponder also note that an immune response in the human may have caused a subsequent drop in FIX activity. The co-administration of an immunosuppressant (e.g., cyclophosphamide) is suggested as a possible solution.

The Examiner's citation of Manno et al. (Nature Medicine 12:342-347 (2006)), actually underscores the importance of Applicants' invention when it describes that "future studies in humans may require immunomodulation to achieve long-term expression" (see, e.g., abstract). Additionally, the methods described in the instant specification can be extrapolated to the treatment of hemophilia in humans. Also, the Examiner's discussion of circulating Factor IX levels on page 10 of the Official Action is irrelevant based on the teachings of Lofqvist et al. discussed above regarding therapeutic levels of Factor IX (i.e., 1% increase results in benefit). Notably, Manno et al. even disclose that therapeutic levels of FIX were obtained in humans. Applicants note that the Examiner states that the reason for the decline in efficacy of FIX expression with increasing size of subject "was not entirely clear even after five years of filing of this application." However, this is completely irrelevant to the instantly claimed invention. The skilled artisan need not know *why* the level of FIX expression may decrease with increasing subject size. Regardless of the reason, therapeutic levels of FIX expression were still obtained in both canines and humans, as described hereinabove. Further, the modulation of the amount of vector

administered is certainly routine to the skilled artisan and cannot be reasonably considered undue experimentation, particularly in view of the references incorporated into the instant application.

The Examiner's citation of Gautam et al. (Am. J. Respir. Med. (2002) 35-46) is irrelevant to the instant invention since the reference contemplates different delivery routes, using different methods, for a different outcome, and is wholly silent with regard to Factor IX therapy. Likewise, Xiao et al. (Mol. Ther. (2000) 1:323-329), cited by the Examiner at page 12 of the Official Action, is not applicable to preventing antibody formation to the transgene delivered via AAV and is silent wholly silent with regard to FIX gene therapy. As such, Xiao et al. is relevant to the instantly claimed methods, particularly in view more relevant references discussed hereinabove.

In light of all of the above, Applicants submit that the references cited by the Examiner do not prove that the prevention of inhibitory antibody formation is not enabled. Furthermore, Applicants submit that the publications cited by the Examiner clearly imply that Factor IX can be delivered *in vivo* in accordance with the methods described in the instant application.

Lastly, Applicants also submit that the Office is inappropriately imposing on the requirements for patentability the standards used to evaluate a drug product for clinical use. Requiring data from human clinical trials to satisfy the enablement requirement is outside the domain of the Office. The Federal Circuit has addressed this issue with respect to developing a drug for clinical use. The Court clearly indicated that testing for the full safety and effectiveness of a potential drug is more properly left to the FDA and that such testing is not required to enable a claim. See In re Brana, 51 F.3d 1560, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) (citing Scott v. Finney, 34 F.3d 1058, 32 U.S.P.Q.2d 1115

(Fed. Cir. 1994)). By invoking these issues, the Office is improperly combining "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption." Id. at page 1567.

The Court's rationale is relevant here. The prosecution history provides data on the efficacy of Applicants' treatment in animals. The Office's requirements for proof of efficacy of the methods of the invention in humans goes beyond the enablement requirement for patentability and is thus improper. However, Applicants have demonstrated the operability of the Factor IX delivery in humans and have enabled the claims for mammals other than the rodents as described hereinabove.

Overall, the experimentation necessary in the present case to practice the claimed methods is merely routine and inherent in the nature of the art. In re Wands, 8 USPQ2d at 1404. Applicants submit that the level of skill in the art of gene therapy is quite high, and the required techniques are familiar to those skilled in this art area. The present inventors have found that immunosuppression is useful to prevent inhibitory antibodies to the gene being delivered to a patient. One skilled in the art, armed with Applicants' specification, is provided sufficient information and guidance to make and use the instantly claimed methods.

In light of the above, Applicants respectfully submit that the skilled artisan could readily practice the invention encompassed by the claims without undue experimentation since the instant specification "provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 8 U.S.P.Q.2d 1400, 1404 (1988). Accordingly, the rejection of the claims under 35 U.S.C. §112, first paragraph is untenable and should be withdrawn.

CONCLUSION

In view of the amendments presented herewith and the foregoing remarks, it is respectfully urged that the rejection set forth in the February 26, 2008, Official Action be withdrawn and that this application be passed to issue.

In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the Examiner is requested to call the undersigned at the phone number given below.

Respectfully submitted,
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Enclosures: Jiang et al., Mol. Therapy (2006) 14:452-455
Lofqvist et al., J. Int. Med. (1997) 241:395-400